Attachment A

Acceptable Industrial Exposure Limit for N-Propyl Bromide

ICF has performed an evaluation of the literature on n-propyl bromide (1-bromopropane, NPB) for the purpose of evaluating its potential metabolites and their expected toxicity following inhalation exposure. This information, in addition to the reports on 28- and 90-day inhalation studies and a two-generation inhalation study with NPB, has been used to derive a recommended acceptable exposure limit (AEL) for the use of NPB in industrial settings. An exposure assessment has also been developed based on workplace monitoring data obtained for NPB in adhesive spray and metal cleaning applications. These values have been compared to the derived AEL.

Recommended AEL:	25 ppm (Midpoint Value of a range based on 8-hour Time Weighted Averages)
Basis:	
Endpoints:	Effects on sperm motility
Study:	An Inhalation Two-Generation Reproductive Toxicity Study of 1-Bromopropane in Rats (WIL 2001)
Protocol:	Whole-body inhalation, 6 hours/day, 7 days/week
Concentrations:	0, 100, 250, 500, or 750 ppm
BMDL:	169 ppm (sperm motility)
NOAEL:	100 ppm
LOAEL:	250 ppm (spermatic and hepatic effects)
BMDL[adj]:	(169 ppm × 6 hours / 8 hours × 7 days / 5 days = 177 ppm)
BMDL[HEC]:	177 ppm
Uncertainty/ Modifying Factors:	3 - animal to human extrapolation 2-3 - sensitive individuals
AEL Range:	18-30 ppm

1. Evaluation of Inhalation Studies with NPB

ICF has conducted a thorough evaluation of the reports on both the 28- and 90-day inhalation studies of NPB provided by EPA. This evaluation included not only a review of the results reported, but also the performance of some additional statistical evaluations.

In a 28-day study (ClinTrials 1997a), Sprague-Dawley rats (10/sex/concentration) were exposed by whole-body inhalation to NPB concentrations of 2,000, 5,000, or 8,000 mg/m^3 (equivalent to 400, 1,000, or 1,600 ppm), 6 hours/day, 5 days/week, for 4 weeks. High-concentration effects included central nervous system (CNS) functional impairment (ataxia, gait incapacity, reduced locomotor activity), increased lacrimation and death. Marginally decreased red blood cells, hemoglobin, and hematocrit were observed in the mid- and high-concentration groups, and decreased bone marrow lymphocytes were observed in the high-concentration animals. Marginally increased relative liver, kidney, brain, and lung weights were reported in the mid- and high-concentration groups. Histopathology changes reported in the high-concentration groups included atrophy of the testes, bone marrow, lymphoid tissues, and olfactory mucosa. Vacuolation was observed in several CNS tissues including the white matter of the brain, in both males and females.

In the 90-day study (ClinTrials 1997b), Sprague-Dawley rats (15/sex/concentration) were exposed by whole-body inhalation to NPB concentrations of 500, 1,010, 2,010, or 3,000 mg/m^3 (100, 200, 400, or 600 ppm), 6 hours/day, 5 days/week, for 13 weeks. Centrilobular vacuolation of hepatocytes was observed in males at the highest two concentrations. Increased liver/body weight ratios were also observed at the higher concentrations. The animals were examined for all of the same endpoints as in the 28-day study, but other than the increased relative liver weights, none of the effects seen in that study were reproduced at any of the concentrations in the 90-day study.

Although different effects were observed in the two studies, ICF does not see any serious inconsistencies. Only one concentration is reproduced between the two studies (2,000 mg/m^3 or 400 ppm). The most sensitive outcome in the 28-day study, slight to mild vacuolation of white matter in the brain, was significantly increased in both male (5/10) and female (4/10) animals exposed to NPB, compared to controls, but there was no clear evidence of a concentration-related response for this endpoint. That is, the various exposed groups were significantly different from the controls but not from each other (males - 0/10, 5/10, 6/10, 6/10; females - 0/10, 4/10, 5/10, 5/10 for controls, 2,000, 5,000, and 8,000 mg/m^3[400, 1000, and 1600 ppm]).

More importantly, similar effects were not observed in the subsequent 90-day study, performed by the same laboratory, in animals exposed to 2,000 or 3,000 mg/m^3 (400 or 600 ppm). Therefore, it is possible that these neurological effects may represent a transient, reversible response. No treatment-related effects on neurological function were observed in the low-concentration (2,000 mg/m^3; 400 ppm) or mid-concentration (5,000 mg/m^3; 1,000 ppm) animals in the 28-day study during an abbreviated functional observational battery (FOB). Functional impairment was only observed in high-concentration males and females (8,000 mg/m^3; 1,600 ppm).

Moreover, no impairment of neurological function, as measured by the FOB, was observed in the 90-day study. Thus, the observed vacuolation, while exhibiting a statistically significant increase in all exposed groups compared to controls, does not appear to have had an impact on organ function or neurological performance of the animals. Therefore, this effect may not necessarily be adverse (US EPA 1994). No other statistically significant, toxicologically relevant changes were observed in low- or mid-concentration animals. Therefore, we conclude that the NOAEL for the 28-day study is 5,000 mg/m^3 (1,000 ppm), with a LOAEL of 8,000 mg/m^3 (1,600 ppm), although it could be argued that only a LOAEL of 2,000 mg/m^3 (400 ppm) was identified by this study, if the reversible CNS vacuolation was considered adverse.

ICF has also re-examined the 90-day study to determine a NOAEL. In conducting our own statistical evaluations of the 90-day study, we re-examined the changes in body weights and organ weights (relative and absolute) reported for both male and female animals in the 90-day study. ICF initially determined whether the data sets were normally distributed before conducting an ANOVA statistical test, and determined that the female absolute liver weights and the male relative liver weights were not normally distributed. ANOVA performed on the remaining data sets did not detect any significant changes in the other endpoints. The Kruskal-Wallis test was performed for the female absolute liver weights and male relative liver weights and found that only the change in male relative liver weights was significant. Dunn's Pairwise Test was then performed on both of these data sets and only the relative liver weights in Groups 4 (2,000 mg/m^3) and 5 (3,000 mg/m^3) males exhibited a statistically significant difference at the $p<0.05$ level, compared with control relative liver weights.

The significant increase in both Groups 4 and 5 is a reflection of slightly decreased body weights with slightly increased absolute liver weights. Histopathologically, the only finding that represented a statistically significant increase ($p<0.05$), was the incidence of slight to mild centrilobular vacuolation (6/15) in the liver of Group 5 (3,000 mg/m^3) male animals. Although some incidence of centrilobular vacuolation (3/15) was observed in Group 4 males, it was not statistically significant. Based on these results, we conclude that the NOAEL for the 90-day study is 2,000 mg/m^3, with a LOAEL of 3,000 mg/m^3.

Kim et al. (1999) conducted a study where groups of Sprague-Dawley rats (10/sex/group) were exposed to 0, 50, 300 or 1,800 ppm NPB, 6 hours/day, 5 days/week, for 8 weeks. Transient decreases in activity and mild ataxia were reported following one hour of exposure (these effects had resolved by one hour post-exposure). The authors reported that body weights were statistically significantly decreased from days 27 and 30, for female and male rats, respectively, until study termination. The authors did not report which treatment groups had decreased body weights; however, based on the figure presented in the article, it is likely that only the high-concentration group was affected. Statistically significant decreases in the white blood cell (WBC) count, red blood cell (RBC) count, hematocrit, and mean corpuscular volume, and significant increases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were reported in the high-concentration males. A significant decrease in WBC and platelet count and significant increases in mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and red cell volume distribution were also observed in the low-concentration males. No statistically significant changes in hematology

were observed in the mid-concentration males. Similar hematological effects were not observed in females, with significant decreases in mean corpuscular volume (mid- and high-concentration groups) and red cell volume distribution (low- and high-concentration groups) being the only significant concentration-related changes reported. Because the hematological changes observed in the male rats did not demonstrate concentration-related trends and were not observed in females, it seems likely that these effects were biological variation rather than treatment-related.

The only statistically significant changes in clinical chemistries observed in male rats were decreases in blood urea nitrogen (BUN; mid-concentration group only), aspartate aminotransferase (AST; mid- and high-concentration groups), alanine aminotransferase (ALT; all groups), and lactate dehydrogenase (LDH; high-concentration group) levels. In females, creatinine and total bilirubin were significantly decreased in the high-concentration group, while ALT was decreased in the mid- and high-concentration groups. Decreases in enzyme (AST, ALT, LDH) and creatinine levels are not considered to be toxicologically significant and we considered these effects to be due to biological variation rather than related to treatment. Urinalysis data were not reported in the study, although the authors did note that urobilinogen levels were significantly decreased in the high-concentration males, but were increased in the mid- and high-concentration females. Urine ketone levels were increased in the high-concentration males and females and in the mid-concentration females. Bilirubin levels and leukocyte numbers were increased in the urine of the high-concentration females. The changes in clinical chemistry and urinalysis parameters were considered to be due to biological variation, rather than treatment-related.

There were no gross lesions reported at necropsy; however, relative testicular and ovarian weights were significantly increased in the high-concentration males and females, respectively. Relative kidney weights were significantly increased in the high-concentration males and females, and relative liver and brain weights were increased in the mid- and high-concentration males. Relative liver weights were also increased in the high-concentration females. Given that the authors reported that exposures to NPB were associated with decreases in body weights, it seems likely that the changes in relative organ weights were a reflection of the decreased body weights rather than related to treatment. Histopathology incidence data were not provided in the report, although the authors did note that cytoplasmic vacuolation in the hepatocytes around the central vein (not concentration-related) and renal tubular casts were observed in the high-concentration females.

Because key data, specifically the histopathology incidence and body weight data, were not provided by Kim et al. (1999), it is difficult to draw firm conclusions from this study and to determine a NOAEL for the study. The hematological and clinical chemistry effects and the changes in relative organ weights were not considered to be related to treatment for reasons discussed above. The results of this study appear to support the results of the 90-day study (ClinTrials 1997b), where increases in cytoplasmic vacuolation of the hepatocytes in the centrilobular region and increased relative liver weights were reported.

Other studies have been conducted where the potential toxicity of NPB has been evaluated following inhalation exposures (Ichihara et al. 1998, 1999; Kim et al. 1996; Wang et al. 1999; Yu

et al. 2001). In a study by Ichihara et al. (1998), male Wistar rats (9/group) were exposed via inhalation to NPB at concentrations of 0 (air only), 200, 400, or 800 ppm, 8 hours/day, 7 days/week, for 12 weeks. Endpoints evaluated were fore- and hindlimb grip strength, tail latency, and mean conduction velocity of the peripheral nerves. Sperm counts and sperm motility were also evaluated. The study authors reported a concentration-dependent decrease in grip strength and a decrease in mean conduction velocity and distal latency in the high-concentration rats; however, it was unclear if these data were analyzed statistically. In rats exposed to 400 or 800 ppm, decreases in sperm counts and motility were reported. Based on the effects on sperm counts and motility, a NOAEL for this study would be 200 ppm.

In a study by Yu et al. (2001), groups of nine male Wistar rats were exposed to 0 (air control) or 1,000 ppm NPB 8 hours/day, 7 days/week, for 5 or 7 weeks. Overt neurotoxicity (hindlimb paralysis) was observed in 6 of the exposed rats after 5 weeks of exposure, at which time they were sacrificed. The remaining 3 rats developed hindlimb paralysis after 6 weeks of exposure and were sacrificed after 7 weeks of exposure. The mean body weights in the exposed rats were significantly decreased when compared with controls. Motor nerve conduction velocity was significantly decreased and distal latency was significantly increased (when measured after 4 weeks of exposure) in the treated rats when compared with controls. Peripheral nerve degeneration and axonal swelling in the spinal cord (observed microscopically) were reported in the treated rats. No microscopic treatment-related lesions were reported in the testes, liver, kidney, or bone marrow. Exposure to NPB caused a significant increase in mean corpuscular volume; no changes were observed for the other measured hematological parameters.

Another study by Ichihara and colleagues (Ichihara et al. 2000a) was identified. This study also exposed groups of nine male Wistar rats to 0 (air control), 200, 400, or 800 ppm NPB for 8 hours/day, 7 days/week, for 12 weeks. It is unclear if this is a separate experiment from that published in 1998, or simply a reiteration of the earlier reproductive data with additional data from supplemental analyses. Significant decreases in absolute and relative seminal vesicle weights were observed in all treatment groups. Significant decreases in mean body weights and absolute epididymal weights were reported for the mid- and high-concentration groups and significant decreases in absolute prostate and relative epididymal weight were reported for the high-concentration group. Relative liver weights were significantly increased in the mid- and high-concentration groups, likely due to the decreased body weights at these concentrations. Significant decreases in the sperm count and the percentage of motile sperm relative to controls were observed in the mid- and high-concentration groups, while significant increases were observed in tailless sperm at the mid- and high-concentrations and in sperm with abnormally-shaped heads at the high-concentration. While exposure to NBP did not affect the count of various spermatogenic cells in the stage VII seminiferous tubules, the 800 ppm concentration did result in a significant increase in degenerating spermatocytes in these tubules (when expressed both as cells/tubule and cells/100 Sertoli nuclei). Further, exposure to both 400 and 800 ppm NBP resulted in significant increases in retained elongated spermatids at postspermiation stages IX, X, and XI. Circulating testosterone was significantly decreased at 800 ppm. A NOAEL of 200 ppm was identified based on effects on sperm count, shape, motility, and maturation.

In a separate publication based on the same study, Ichihara and colleagues (2000b) reported that the male rats showed a dose-dependent peripheral neuropathy evidenced by an inability to stand still on a plane and weak kicking ability in the 800 ppm group. Fore- and hind-limb grip strength was tested every 4 weeks during the 12-week exposure. Following 4 weeks of exposure, hind-limb grip strength was significantly decreased at ≥200 ppm; this parameter was significantly decreased only in the 800 ppm group at 8 weeks, and in the 400 and 800 ppm groups at 12 weeks. Forelimb grip strength decreased throughout the study at ≥400 ppm and was significantly different from controls at 8 and 12 weeks at 800 ppm and at 8 weeks at 400 ppm. Mean conduction velocity was significantly decreased at 800 ppm at 8 and 12 weeks, while distal latency was significantly increased at 800 ppm at 4, 8, and 12 weeks. Histopathology revealed disruption of the myelin sheath of the posterior tibial nerve at 800 ppm and a dose-dependent increase in the swelling of preterminal axons in the gracile nucleus. Plasma creatine phosphokinase was decreased dose-dependently, with significant decreases reported at ≥400 ppm. Assuming the decrease in hindlimb grip strength at 4 weeks is a transient response, a NOAEL for this study would be set at 200 ppm.

A recent study has been reported by Sekiguchi et al. (2002) that investigated the potential effect of inhalation exposure to 1-bromopropane on reproductive function. This study exposed female F344 rats (aged 7-8 weeks) to concentrations of 0, 50, 200, and 1000 ppm for 8 hours/day for at least 21 days. The actual concentrations of NPB were measured every 30 minutes by gas chromatography/flame ionization detection and were reported to be 50.7±1.1, 205.5±5.1, and 1022.5±38.4 ppm, respectively, in the dosed groups. The number of females in the control, low-, mid-, and high-dose groups was 7, 7, 7, and 8, respectively. The study authors measured body weights and numbers of estrous cycles (by vaginal smear) daily throughout exposure. Following the exposure period the animals were sacrificed; ovary and uterine weights and the number of ovulated ova were calculated for each rat. The total number of estrous cycles per dose group, the number of cycles per rat, and the days/cycle were comparable for all dose groups. The number of rats with cycles equaling or exceeding six days in length was similar in the control, low-, and mid-dose groups, (2, 3, and 2, respectively), and was slightly higher (5) in the high-dose group. Similarly, the number of cycles that were ≥6 days in length was 3, 4, 3, and 7 in the control, low-, mid-, and high-concentration groups, respectively. None of the slight increases reached statistical significance. Slightly lower numbers of rats (6, 5, 7, and 7 in the control, low-, mid-, and high-concentration groups, respectively) were measured for body and organ weights and reproductive physiology. No effects on body weight, ovary and uterine weight (absolute or relative) or the number of ovulated ova resulted from NPB exposure. A NOAEL of 1023 ppm (based on the average of actual exposure concentrations) was identified for this study.

In a series of abstracts presented at the Annual Meeting of Japan Society for Occupational Health, Ichihara and colleagues (Ichihara et al. 1999; Wang et al. 1999) presented additional data on the potential toxicity of NPB. English translations were available for some of these abstracts and are discussed below. The Ichihara data are the same as that reported in the article published in 2000 (Ichihara et al. 2000a).

Wang et al. (1999) conducted a study where groups of Wistar rats were exposed to 0 (air control), 200, 400, or 800 ppm NPB, 8 hours/day, 7 days/week, for 1 week. It should be noted

that the text of the abstract notes that there were nine rats/group; however, the data presented in Tables 1 and 2 indicate that each group consisted of only 8 animals. Statistically significant decreases in terminal body weights, absolute prostate weight, and absolute and relative seminal vesicle weights were reported in the high-concentration group. No significant differences were reported for relative prostate weight or absolute epididymal weight. There were no statistically significant changes in sperm counts. The percentage of tailless sperm (high-concentration group) and abnormal sperm (mid- and high-concentration groups), however, were significantly increased. In addition, Wang et al. (1999) reported that the percentage of motile sperm was significantly decreased in all treated groups. It should be noted that other data from the same laboratory where male rats were exposed for 12 weeks also revealed a dose-response relationship for sperm abnormalities (see discussion of Ichihara et al. 2000a, above).

Other abstracts were presented by Ichihara and colleagues at the Annual Meeting of Japan Society for Occupational Health. The exposures were very high ($\geq$1,500 ppm), and therefore not relevant to human exposure, or English translations were not available. Therefore, these data were not used in this risk assessment. Moreover, the confidence in the unpublished data presented by Ichihara et al. (1999) and Wang et al. (1999) is low for a number of reasons. Specifically, it was unclear if comparisons were made to concurrent controls, and there were discrepancies in the number of animals used. In addition, there were no indications that these particular studies complied with Good Laboratory Practice (GLP) guidelines and that appropriate quality assurance/quality control reviews were made.

Based on an abstract by the Japan Bioassay Research Center (unpublished), Crj:CD(SD)IGS rats (10/sex/group) were exposed whole body to concentrations of 0, 94, 188, 375, 750, or 1,500 ppm NPB, 6 hours/day for 42 days to evaluate reproductive toxicity. Males were exposed 14 days prior to mating, 14 days during mating, and 14 days following mating. Females were exposed 14 days prior to mating, 14 days during mating, and until the 19th day of pregnancy. Endpoints evaluated included survival, general condition, body weight, food consumption, urinalysis, hematoscopy, hemato-biochemical test, dissection tests, organ weight, histopathological tests as observation/tests for repeated dose toxicity and observation of periodicity, number, motility, and deformation of spermatozoa, mating rate, impregnation rate, observation of delivery and nursing conditions (pregnancy term, number of corpora lutea, number of implantations, implantation rate, delivery rate), and observation of the newborn pups for reproductive toxicity. The authors reported decreases in spermatozoa in the upper body of the spermary, motility, implantation rate, and number of fetuses following exposure to $\geq$750 ppm NPB and liver effects at >750 ppm NPB. An increase in total protein and albumin levels was reported at 375 ppm NPB and a decrease in FSH levels in males exposed to >188 ppm NPB was reported. The data presented in the abstract were insufficient to determine a NOAEL. Based on the authors' description of the results, however, the effects reported in this study were similar to effects reported in other NPB toxicity studies.

The collective body of data from animal studies involving inhalation exposures to NPB (Ichihara et al. 1998, 1999, 2000a; Wang et al. 1999) indicate that the compound is a potential reproductive toxin. Although the majority of data are consistent in their findings, the studies have limitations that preclude their use in a quantitative risk assessment. In addition, results from

studies conducted with the structurally analogous chemical 2-bromopropane (2-BP) have indicated adverse effects on the reproductive system. A two-generation study was designed to provide better data for quantitatively evaluating the potential reproductive toxicity of NPB. Exposure to 2-BP has been associated with amenorrhea and testicular toxicity in exposed workers (Kim et al. 1996), with similar effects observed in animals (Ichihara et al. 1996; Takeuchi et al. 1997). Therefore, in the two-generation reproductive study, endpoints related to these effects (e.g., measurements of estrous cycle length and evaluation of sperm morphology and motility) were evaluated as well.

In order to analyze appropriate inhalation concentrations in the two-generation study, a range-finding study was performed in rats (Rodwell 2001). Rodwell et al. (2001) exposed 25 pregnant rats (Crl:CD® [SD] IGS BR strain) to the following exposure concentrations of NPB for 6 hours/day from gestation day 6 to gestation day19: 0 (air control), 100, 498, and 996 ppm. Females at the two highest concentrations exhibited treatment-related decreases in body weight, body weight gain, and feed consumption. Exposure to nPB did not result in any changes in the following reproductive or developmental parameters: pregnancy rates; implantation data; sex distribution; and fetal external, skeletal or visceral malformations. Statistically-significant decreases in fetal weight were observed at all exposure concentrations of nPB. The study authors indicated, however, that this decrease might be an artifact of the sampling process used to select fetuses for organ sampling. For example, one or two control females were saved for sacrifice and caesarean section at the end of the day in order to harvest control fetal organs in the event of an effect in treated fetuses. This delay in sacrifice of the control females reportedly resulted in an average increase in fetal weight of 0.2 g, which was the weight difference observed between the treated and control groups.

The study authors indicated that when this effect was taken into account, the 498 ppm group might have had a slight decrease in mean fetal body weight, while the decrease in mean fetal body weight at 996 ppm was believed to be the result of maternal toxicity. A significant and dose-related increase in reduced ossification of the fetus (on a per litter basis) was observed at 498 and 996 ppm. Further, there was a statistically-significantly increased incidence in bent ribs in the 996 ppm exposure group that was considered to be exposure-related. Slight, but not statistically significant, increases in litter incidences of unossified hyoid body/arches, and unossified sternebra(e) 5 and/or 6 were observed at the highest concentration, but were believed to be due to maternal toxicity (e.g., decreased maternal body weight). Based on the maternal and fetal effects observed at 498 ppm, the NOEL for this study is 100 ppm.

In the two-generation study (WIL 2001), groups of 25 male and female rats were exposed to NPB via whole-body inhalation. The F_0 animals were exposed to target air concentrations of 0, 100, 250, 500, or 750 ppm NPB 6 hours/day, 7 days/week, for at least 70 days prior to mating. The F_1 animals were exposed to 0, 100, 250, or 500 ppm, because infertility in the F_0 750 ppm group precluded having an F_1 750 ppm group. Exposure for male animals of both generations continued throughout mating to the day prior to study termination. Exposure for female animals in both generations continued throughout mating and gestation through gestation day 20, and after parturition on lactation day 5 through the day prior to study termination.

In the F_0 animals, mean body weights were generally reduced throughout the premating period for the 750 ppm males and throughout the latter half of this period for the 750 ppm females. The major effect observed in this exposure group was 100% infertility, resulting in no F_1 offspring for this group. In the 500 ppm group of the F_0 generation, male and female fertility indices exhibited a statistically significant decrease. Based on statistical analyses conducted by ICF, a significant increase in mean estrous cycle length was observed in F_0 females exposed to $\geq$500 ppm NPB. A significant decrease in the number of former implantation sites was also reported in F_0 females exposed to $\geq$500 ppm as well as in F_1 females. Significant changes in spermatogenic endpoints reported included decreases in sperm motility in the F_1 generation following exposure to $\geq$250 ppm and in the F_0 generation following exposure to $\geq$500 ppm. Significant decreases in the number of normal sperm and absolute and/or relative epididymal weights were also observed in both generations following exposure to $\geq$500 ppm, as well as a significant decrease in the number of offspring. These reproductive effects were similar to those reported in the Ichihara et al. (1998; 2000a) and Wang et al. (1999) studies.

Many significant changes in organ weights were noted in the treated groups compared to the untreated controls. In general, most of these organ weight changes were in absolute values, but were not significant when weights were expressed relative to body weight and had no correlating macroscopic or microscopic changes. Therefore, the authors concluded that the biological significance of many of these changes is unclear. These absolute organ weight changes included decreased brain weight in F_0 ($\geq$250 ppm) and F_1 ($\geq$100 ppm) males, decreased prostate weights in F_0 ($\geq$250 ppm) and F_1 (500 ppm) males, decreased pituitary weights in F_0 (750 ppm) and F_1 (500 ppm) males, and decreased seminal vesicle weights in F_0 (750 ppm) and F_1 (250 ppm) males. In F_1 males, a statistically significant increase in absolute and relative thymus weight was observed in the 500 ppm group; however, there were no corresponding microscopic changes.

Hepatic effects similar to those reported in the 90-day study (ClinTrials 1997b) were observed in both F_0 and F_1 males and females. Increases in mean relative liver weights were observed in F_0 and F_1 males and females following exposure to $\geq$500 ppm. Corresponding increases in the incidence of minimal to mild centrilobular hepatocellular vacuolation or increased glycogen were observed at $\geq$250 ppm in males and $\geq$500 ppm in females. Microscopic changes in the kidney were also observed and included increases in the incidence of minimal to mild pelvic mineralization and secondary transitional epithelial hyperplasia following exposure to 500 ppm and greater in both generations of males and females. A NOAEL for this study was 100 ppm, with a LOAEL of 250 ppm for the spermatogenic effects (significant decreases in sperm motility), as well as liver effects observed in male rats.

The two-generation study in rats (WIL 2001) was chosen as the most appropriate study to use for the development of an AEL. This study was chosen for several reasons: (1) the exposure groups were larger and gave more robust statistical results; (2) a lower concentration range was used (which would likely be more comparable to occupational exposures); (3) exposures covered preconception, gestation, and preweaning periods, thus ensuring that potential effects on both generations could be assessed, including fertility index. Because the protocol involves a postnatal as well as an *in utero* exposure to the first generation, it provides the opportunity to examine the susceptibility of the immature/neonatal animal and potential persistent reproductive effects.

Reproductive and liver toxicity were chosen as the most sensitive endpoints of toxicity because they occurred at the lowest concentration (250 ppm) in the two-generation study. Similar reproductive and liver effects were reported in previously reviewed studies. ICF did not consider neurological effects to be one of the most sensitive endpoints because, although neurotoxicity was reported in two studies (Ichihara 1998, 2000b), no neurological impairment was seen in a 90-day study conducted according to GLP standards (ClinTrials 1997b).

2. Evaluation of Other Studies of NPB Toxicity

A vapor-phase Ames test with NPB reported positive results with two out of five strains of *Salmonella typhimurium*, both with and without the addition of rat liver S9 fraction metabolic activation (Barber et al. 1981; Barber and Donish 1982). These findings have been confirmed by more recent unpublished studies (Elf Atochem 1996) but not by others (Elf Atochem 1994). Unpublished studies of *in vivo* micronucleus formation (Elf Atochem 1995a) indicate that NPB is not clastogenic, and a published dominant lethal assay with NPB was also negative (Saito-Suzuki et al. 1982).

In a cell death bioassay using cultured human liver cells (HepG2 hepatoma), the cytotoxicity of NPB was evaluated at concentrations $\leq$ 500 ppm (Stelljes 2001). Results of the bioassay indicated that NPB was cytotoxic (measured as decreased cell viability) at the highest concentration tested (500 ppm). There were no positive responses reported at any concentration for tests that evaluated enzyme function, DNA damage, or DNA damage and repair when tested at concentrations up to 500 ppm.

The acute toxicity of NPB in Sprague-Dawley rats has been studied for inhalation (Elf Atochem 1997), oral (Elf Atochem 1993), and dermal (Elf Atochem 1995b) routes of exposure. The 4-hour LC_{50} for inhalation of NPB was 35,000 mg/m^3 (Elf Atochem 1997), with death resulting from pulmonary edema. The LD_{50} for gavage dosing of NPB was greater than 2,000 mg/kg (Elf Atochem 1993). No abnormalities were found on macroscopic examination of the 10% of the animals dosed at 2,000 mg/kg that died. Animals receiving 2,000 mg/kg NPB dermally (with occlusion of the exposure area) showed no cutaneous reactions and no evidence of toxicity (Elf Atochem 1995b). A skin sensitization test in Guinea pigs was also negative (Elf Atochem 1995c).

In a study by Oh et al. (1998), 6-week or 8-month-old male ICR mice were fed 0.27 g NPB or 4 mL/kg NPB in corn oil via intraperitoneal injection for 5 days. After terminal sacrifice, brain tissues were collected and analyzed for beta-amyloid protein. Beta-amyloid protein levels were increased in the 8-month-old mice, when compared with beta-amyloid protein levels in the 6-week-old mice. There were no differences reported in the brain levels of beta-amyloid protein in 6-week-old mice that received NPB when compared to untreated controls. However, beta-amyloid protein levels in the treated 8-month-old mice were increased above the levels reported in the controls.

Other toxicity studies have been conducted to evaluate the potential effects of NPB on the nervous system (Fueta et al. 2000; Zhao et al. 1999). These studies have limited usefulness because they involved exposures to very high concentrations of NPB (1,500 ppm; Fueta et al. 2000) or exposure was via subcutaneous injection (Zhao et al. 1999).

3. Evaluation of the Literature on NPB Metabolism and Pharmacokinetics

A diagram of the metabolism of NPB is shown in a figure at the end of this section. NPB is primarily metabolized by conjugation with glutathione (Jones and Walsh 1979; Khan and O'Brien 1991), and micromolar concentrations of NPB have been shown to deplete glutathione *in vitro* (Khan and O'Brien 1991). Oxidative metabolism of the 2- and 3-positions may also occur (Jones and Walsh 1979). Oxidation at the 2-position would lead to the formation of the carcinogenic epoxide, 1,2-epoxypropane, which is further metabolized by glutathione conjugation. Theoretically, the epoxide could also be derived from the reductive dehalogenation of NPB to propene and subsequent P450 oxidation, but there is no evidence to support a quantitatively important role for this pathway *in vivo* (Jones and Walsh 1979).

Tissue partition coefficients for NPB in the rat, as well as blood-air partition coefficients in the human, have been measured (Gargas et al. 1989). The reported blood-air partition coefficients in the rat and human were 11.7 and 7.1, respectively, indicating a lower potential for bioaccumulation of NPB in the human than in the rat.

By analogy to similar halogenated hydrocarbons, it can be assumed that while NPB is likely to be absorbed through the skin, its bioavailability would be low (due to its high vapor pressure) except for prolonged exposure of the skin to liquid, as when the exposure area is occluded.

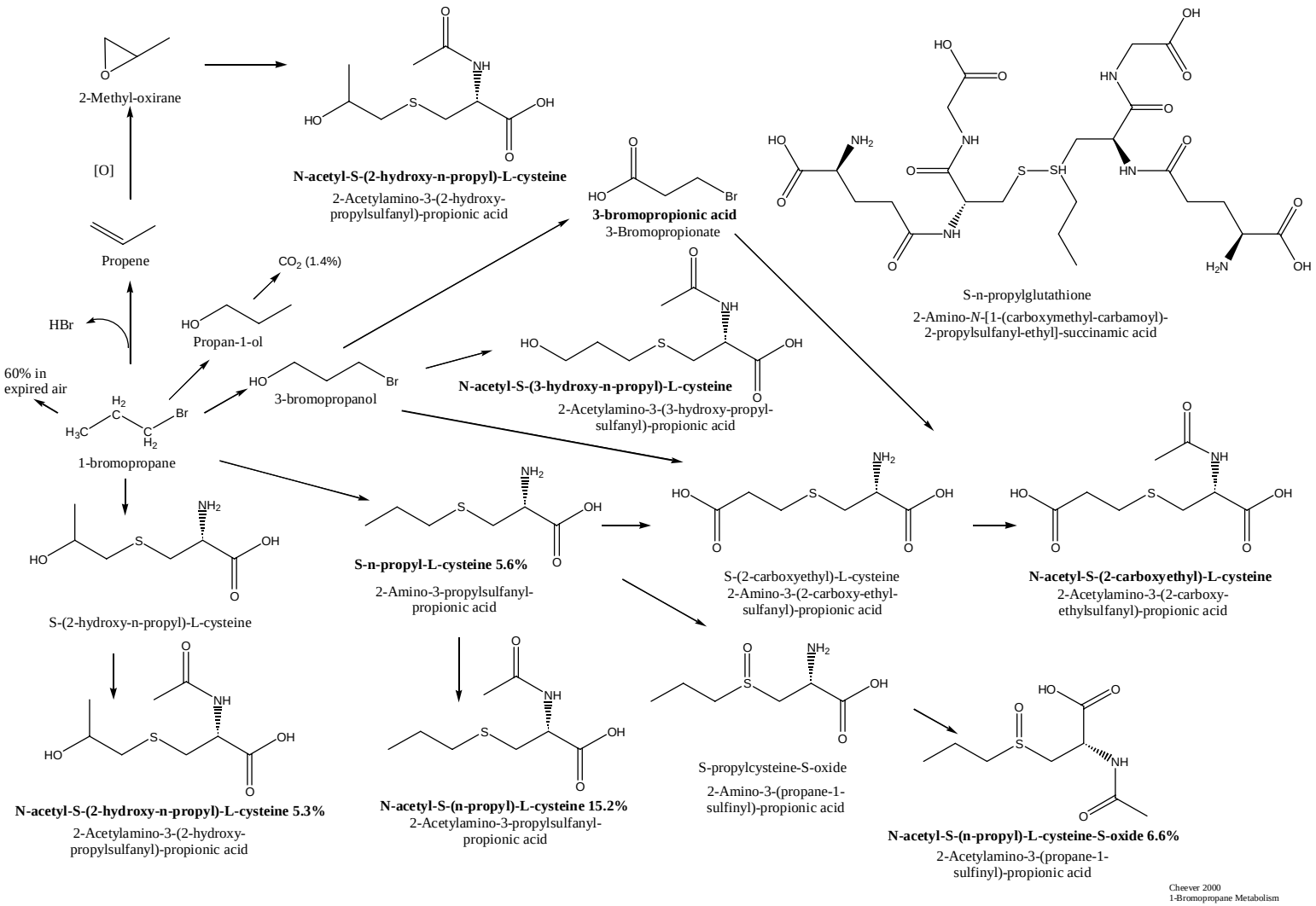
Finally, it should be noted that bromide (which is an anesthetic) is produced by the metabolism of NPB, and that the half-life of bromide in the human is quite long compared to other species. Thus it seems possible that repeated human exposure to relatively high concentrations of NPB could produce symptoms of anesthesia that would not be observed in similar exposures of experimental animals. Presently, adequate data on the production of bromide from NPB do not exist to quantitatively evaluate this possibility.

4. Evaluation of Data on Structural Analogues of NPB

Acute exposures to volatile halogenated hydrocarbons at concentrations on the order of one percent have frequently been associated with cardiac sensitization (Hermann and Vial 1935). It is not expected that exposures to NPB at such high concentrations would occur.

A closely related compound, ethyl bromide, is weakly carcinogenic in rodents (Haseman and Lockhart 1994), and 2-bromopropane (2BP) is weakly mutagenic (Maeng and Yu 1997). Moreover,

Metabolism of 1-Bromopropane (Urinary product names in bold)



as mentioned above, one of the potential metabolites of NPB, propylene oxide, is also carcinogenic. The available short-term genotoxicity data for NPB, described in Section 2, however, do not support the need for significant concerns regarding the potential carcinogenicity/genetic toxicity of NPB.

Occupational exposure to the related isomer 2BP has been associated with anemia and reproductive toxicity in both men and women (Kim et al. 1996). The reproductive and hematopoietic effects of 2BP have also been demonstrated in animal studies (Takeuchi et al. 1997). In particular, studies with male rats exposed to 300 ppm (1,500 mg/m^3) 2BP, 8 hours/day, 7 days/week, for 9 weeks demonstrated decreased red cell counts, testicular weights, sperm counts, and sperm motility (Ichihara et al. 1996,1997), while similar 9-week studies with female rats reported changes in estrous cycling at 300 ppm, but not at 100 ppm (Kamijima et al.1997a,b).

5. Recommendation of an Industrial Exposure Guideline

The spermatic and hepatic effects reported in the 90-day study (ClinTrials 1997b) and the two-generation study (WIL 2001) were considered the critical endpoints. Other effects were reported in the toxicity studies with NPB; however, these effects were observed following exposures to higher concentrations than the concentrations that produced effects on sperm motility or in the liver. Therefore, the data sets for these endpoints were selected for Benchmark dose-response modeling.

The Benchmark Dose (BMD) approach, an alternative to the traditional NOAEL/LOAEL approach, is an estimate of a dose corresponding to a pre-defined risk or response level. That estimation is typically accomplished through dose-response modeling, so that a model-based determination of the dose corresponding to a level of risk or response can be made. The BMD is the central estimate of the dose expected to yield the Benchmark Response, or BMR, which is the response level of interest. This level is typically a 10% response, but in developmental studies, a lower response rate of 5% is often estimated (US EPA, 1995). For the purposes of comparing the BMDs for sperm and liver effects, BMD values for a 10% response rate were calculated in this analysis. It is often the case that the estimate of the dose used to define the BMD represents a “lower bound” on the value of the dose that corresponds to the response level of interest. The selection of this lower bound value is to account for the uncertainty in the model based on several factors such as small sample size, etc. The abbreviation BMDL is used to distinguish this “lower bound” estimate from the “best estimate” BMD or estimate of central tendency. A BMDL is often used as a point of departure (POD) for developing reference values such as AELs or RfDs. Compared to the NOAEL/LOAEL approach, advantages of the BMD approach are that the BMD does not have to be one of the dose groups employed in the study, it utilizes more information from the dose-response curve, and a BMD and a BMDL can usually be calculated even in studies where a NOAEL could not be identified (i.e., in studies where responses in the lowest group tested were considered adverse).

5.1 Benchmark Dose Methods

The data sets considered for dose-response modeling include both quantal and continuous endpoints. The hepatocellular effects (centrilobular vacuolation) observed in males and females of the F_0 and F_1 generations in the WIL (2001) study and in males in the ClinTrials (1997b) study were the quantal effects modeled. Sperm motility measurements in F_0 and F_1 males from WIL (2001) were the continuous effects modeled. The EPA's Benchmark Dose Software (BMDS) (US EPA 2000, Williams and Kelley 1997) was used to accomplish all of the model fitting and BMD estimation. The methods and models applied to both quantal and continuous endpoints are presented here.

5.1.1 Quantal Models

Seven of the nine quantal models implemented in the BMDS package were used to represent the dose-response behavior of the quantal endpoints. Specifically, the models used were the gamma model, the logistic and log-logistic models, the probit and log-probit models, the multistage model, and the Weibull model. Two other models, the linear and the quadratic models, were not fit to the data because they are special cases of both the multistage and the Weibull models. If the fitting of the multistage or Weibull models resulted in a linear or a quadratic form, then those results were used; otherwise, the linear or quadratic models would not provide a fit as good as the multistage or Weibull model and so were not separately obtained.

The equations defining each of these models are presented here (US EPA 2000). In all of the following, P(d) represents the probability of response (i.e., adverse effect) following exposure to "dose" d. In all of these models, α, β, and γ are model parameters estimated using maximum likelihood techniques, as described in Table 5.1.1.

When fitting all of the above-mentioned quantal models, maximum likelihood methods were used to estimate the parameters of the models. That method maximizes the log-transformed likelihood of obtaining the observed data, which is (except for an additive constant) given by

$$L = \Sigma[n_i \bullet \ln\{P(d_i)\} + (N_i - n_i) \bullet \ln\{1 - P(d_i)\}]$$

where the sum runs over I from 1 to k (the number of dose groups), and for group I, d_i is the dose (exposure level), N_i is the number of individuals tested, and n_i is the number of individuals responding (US EPA 2000).

5.1.2 Continuous Models

The continuous endpoints of interest with respect to toxicity were quantitatively summarized by group means and measures of variability (standard errors or standard deviations). The models used to represent the dose-response behavior of those continuous endpoints are those implemented in EPA's BMDS (US EPA 2000). These models were the power model, the Hill model, and the polynomial model. These mathematical models fit to the data are defined here. In all cases, $\mu(d)$ indicates the mean of the response variable following exposure to "dose" d.

Table 5.1.1
Model Equations Used in BMD Calculations

Model	Equation	Conditions
gamma	$P(d) = \gamma + (1 - \gamma) \cdot (1/\Gamma(\alpha)) \cdot \int t^{\alpha-1} e^{-t} dt$	$0 \leq \gamma < 1$, $\beta \geq 0$, and $\alpha \geq 1$. $\Gamma(x)$ is the gamma function, and the integral runs from 0 to βd.
logistic	$P(d) = [1 + \exp\{-(\alpha + \beta d)\}]^{-1}$	$\beta \geq 0$
log-logistic	$P(d) = \gamma + (1 - \gamma) \cdot [1 + \exp\{-(\alpha + \beta \ln(d))\}]^{-1}$	The log-logistic model has much the same form as the logistic model except when d = 0, in which case $P(d) = \gamma$. In this case $\beta \geq 0$, and for the background parameter γ, $0 \leq \gamma < 1$.
probit	$P(d) = F(\alpha + \beta d)$	F(x) is the standard normal cumulative distribution function and $\beta \geq 0$.
log-probit	$P(d) = \gamma + (1 - \gamma) \cdot F(\alpha + \beta \cdot \ln(d))$	The log-probit model has a form similar to the probit model except when d = 0, in which case $P(d) = \gamma$. Here $0 \leq \gamma < 1$, and $\beta \geq 1$.
multistage model	$P(d) = \gamma + (1 - \gamma) \cdot (1 - \exp\{-(\beta_1 d + \beta_2 d^2 + ... + \beta_n d^n)\})$	All the β parameters are restricted to be nonnegative and $0 \leq \gamma < 1$. The degree of the multistage model (the highest power on dose in the above equation, n) was set equal to one less than the number of dose groups in the experiment being analyzed.
Weibull model	$P(d) = \gamma + (1 - \gamma) \cdot (1 - \exp\{-\beta d^{\alpha}\})$	The background parameter γ is restricted to fall between 0 (inclusive) and 1, and β is greater than or equal to 0. For these analyses, the parameter α is constrained to be greater than or equal to 1.[1]

[1]The linear model is a special case of the Weibull model obtained by fixing the parameter α equal to 1. The quadratic model is a special case of the Weibull model obtained by fixing the parameter α equal to 2.

The power model is represented by the equation:

$$\mu(d) = \gamma + \beta d^{\alpha}$$

where the parameter $\alpha > 0$. [The linear model is obtained when α is fixed at a value of 1. The linear model was not separately fit to the data; if the result of fitting the power model does not result in the linear form, $\alpha = 1$, then the linear model does not fit as well as the more general power model, by definition.]

The Hill model is given by the following equation:

$$\mu(d) = \gamma + (vd^n) / (d^n + k^n)$$

where the parameters n and k >0. The power n must be ≥ 1.

The polynomial model is defined as

$$\mu(d) = \beta_0 + \beta_1 d + ... + \beta_n d^n$$

where the degree of the polynomial, n, was set equal to one less than the number of dose groups in the experiment being analyzed. For these analyses, the values of the β parameters allowed to be estimated were either all >0 or all <0 (as dictated by the data set being modeled, i.e., >0 if the mean response increased with increasing dose or <0 if the mean response decreased with increasing dose).

In the case of continuous endpoints, one must assume something about the distribution of individual observations around the dose-specific mean values defined by the above models. The assumptions imposed by BMDS were used in this analysis, i.e., individual observations were assumed to vary normally around the means with variances given by the following equation:

$$\sigma_i^2 = \sigma^2 \cdot [\mu(d_i)]^\rho$$

where both σ^2 and ρ were parameters estimated by the model.

Given the above assumptions about variation around the means, maximum likelihood methods were applied to estimate all of the parameters, where the log-likelihood to be maximized is (except for an additive constant) given by

$$L = \sum [(N_i/2)\cdot\ln(\sigma_i^2) + (N_i - 1)s_i^2/2\sigma_i^2 + N_i\{m_i - \mu(d_i)\}^2/2\sigma_i^2]$$

where N_i is the number of individuals in group I exposed to dose d_i, and m_i and s_i are the observed mean and standard deviation for that group, respectively. The summation runs over I from 1 to k (the number of dose groups).

5.2 Goodness-of-Fit Analyses

For the quantal models, goodness of fit was determined by the modeling software using the chi-square test. This test is based on sums of squared differences between observed and predicted numbers of responders. The degrees of freedom for the chi-square test statistic are equal to the number of dose groups minus the number of parameters fit by the method of maximum likelihood (ignoring those parameters that are estimated to be equal to one of the bounds defining their constraints -- see the discussion above about constraints imposed on the model parameters). When the number of parameters estimated equals the number of dose groups, there are no degrees of freedom for a statistical evaluation of fit.

For the continuous models, goodness of fit was determined based on a likelihood ratio statistic. In particular, maximized log-likelihoods associated with the modeling were sequentially compared. First, the log-likelihood obtained when the variances were modeled as described above (but with means that are independent from one dose group to another; log- likelihood A) was compared to the log-likelihood associated with the model that assumed both means and variances were completely independent from one dose group to another (log-likelihood B). It is always the case that the log-likelihood B will be at least as great as log-likelihood A, but if the description of the variance does a "reasonable" job of fitting the data, the difference between the two log-likelihoods will not be too great. Second, log-likelihood A was compared to the log-likelihood associated with the model fit (log-likelihood C); such a model has variation in the variances as in log-likelihood A but also has the model-defined definition of the means as a function of dose. Again, if the model predictions are "reasonable," the difference between log-likelihoods A and C will not be great. Formal statistical tests reflecting this sequence of comparisons use the fact that twice the difference in the log-likelihoods is distributed as a chi-square random variable. The degrees of freedom associated with the chi-squared test statistics are equal to the difference between the number of parameters fit by the two models being compared (including the parameters σ^2 and ρ defining how variances change as a function of mean response level). If the results of both tests in the sequence yield p-values ≥ 0.05, then the model was determined to adequately fit the data.

Visual fit, particularly in the low-dose region, was assessed for models that had acceptable global goodness of fit. Acceptable global goodness of fit was either a p-value ≥ 0.1, or a perfect fit when there were no degrees of freedom for a statistical test of fit. Local fit was evaluated visually on the graphic output, by comparing the observed and estimated results at each data point.

Goodness-of-fit statistics are not designed to compare different models, particularly if the different models have different numbers of parameters. Within a family of models, adding parameters generally improves the fit. BMDS reports the Akaike Information Criterion (AIC) to aid in comparing the fit of different models. The AIC is defined as $-2L+2p$, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model parameters estimated. When comparing the fit of two or more models to a single data set, the model with the lesser AIC was considered to provide a superior fit.

5.3 Definition of the BMR and Corresponding BMD and BMDL

For all of the quantal endpoints analyzed here, the BMDs and BMDLs were defined based on benchmark responses (BMRs) of 10% extra risk (a calculation of 10% extra risk is appropriate for non-cancer systemic effects; US EPA, 1995 BMDLs were defined as the 95% lower bound on the corresponding BMD estimates. Confidence bounds were calculated by BMDS using a likelihood profile method.

For the continuous models, BMDs were implicitly defined as follows:

$$|\mu(\text{BMD}) - \mu(0)| = \delta \cdot \sigma_1$$

where σ_1 is the model-estimated standard deviation in the control group. In other words, the BMR was defined as a change in mean corresponding to some multiplicative factor of the control group standard deviation.

The value of δ used in this analysis was 1.1. This value was chosen based on the work of Crump (1995), who showed that this choice corresponded to an additional risk of 10% when the background response rate was assumed to be 1%, with normal variation around the mean (and constant standard deviation). Although the current analyses allowed for nonconstant standard deviations and estimated extra risk, while the Crump (1995) comparison was based on constant standard deviations and additional risk, the value of 1.1 was used for two reasons. First, the difference between additional and extra risk is small when the background rate is 1% or less, so that the change from additional to extra risk will have minimal impact on the correspondences proven by Crump (1995). Second, there can be no such generic, *a priori* correspondences when standard deviations are allowed to vary in a manner determined only after the model fitting is accomplished. Thus, to avoid data set- and model-specific choices for δ, the correspondences proven by Crump (1995) can be used as the best available, consistent definition of the BMR. The definition of the BMR as a change in mean of 1.1 times the control standard deviation is very close to the default value of 1 standard deviation recommended by recent draft EPA guidelines (US EPA 1999).

As for the quantal models, for all of the continuous models BMDLs were defined as the 95% lower bound on the corresponding BMD. Confidence intervals were calculated using a profile likelihood method.

5.4 Benchmark Dose-Response Modeling Results and Choice of BMDL

The results of the benchmark modeling for all quantal models and all data sets from studies that provide sufficient quantitative data are presented in Table 5.4. The model output is provided in Appendix A and graphs are provided in Appendix B. The following guidelines were used in the selection of BMDLs for each data set:

1. Models with an unacceptable fit (including consideration of local fit in the low-dose region) were excluded. Visual fit, particularly in the low-dose region, was assessed for models that had acceptable global goodness of fit.

2. If the BMDL values for the remaining models for a given endpoint were within a factor of 3, no model dependence was assumed, and the models were considered indistinguishable in the context of the precision of the methods. The models were then ranked according to the AIC, and the model with the lowest AIC was chosen as the basis for the BMDL.

3. If the BMDL values were not within a factor of 3, some model dependence was assumed, and the lowest BMDL was selected as a reasonable conservative estimate, unless it was an outlier compared to the results from all of the other

models. Note that when outliers are removed, the remaining BMDLs may then be within a factor of 3, and so the criteria given in item 2 would be applied.

These criteria were applied to the BMDLs reported in Table 5.4 for each endpoint. For the liver vacuolation endpoint in males or females (F_0 and F_1), all of the models had goodness-of-fit values that were ≤ 3; therefore, the AIC value for each model was used to determine the model (from each data set) that best fit the data. As shown in Table 5.5, following the application of the selection criteria, BMDLs ranging from 110 to 312 ppm were identified. The next step is to choose which data set and model produced the lowest (e.g., most conservative) BMDL value. For liver vacuolation, the lowest BMDL is 110 ppm for the incidence in the F_1 males in the two-generation study. In the case of sperm motility in F_0 and F_1 males, models with the lowest AIC values for each data set were selected (resulting in BMDL values of 282 and 169 ppm). The BMDL for sperm motility in the F_1 generation, 169 ppm, provided the most conservative result. Selecting the lowest BMDLs derived from the various data sets for determining the AEL is consistent with guidance from the US EPA (1995b), and is most protective of human health.

5.5 Derivation of AEL

AELs were derived based on both critical effects (i.e., liver vacuolation and sperm motility) in order to determine the most conservative choice. The BMDL of 110 ppm was based on the incidence of hepatocellular centrilobular vacuolation in F_1 males in the two-generation reproductive study (WIL 2001). Since the desired guideline is for occupational exposure, 5 days/week, 8 hours/day, the exposure duration must be adjusted from a 7 days/week period in the study to the 5 days/week period expected for occupational exposure. Further, an adjustment from the daily animal exposure duration of 6 hours to the human duration of 8 hours is required. Using EPA's RfC dosimetry guidelines for a category 3 gas (US EPA 1994), the human equivalent concentration (HEC) is 110 ppm * (6/8)* (7/5) = 115.5 ppm, as an 8-hour time-weighted average (TWA). The blood-air partition coefficient for NPB in the human (7.1) is less than in the rat (11.7), indicating that the delivered dose in humans is lower than the rat. Therefore, no adjustment for differences in pharmacokinetics was necessary. An uncertainty factor of 2 was applied for animal-to-human extrapolation in consideration of potential differences in pharmacodynamics. Because the *in vitro* data (Stelljes 2001) indicate that human liver cells are no more sensitive than rat liver cells, a full uncertainty factor of 3 for differences in pharmacodynamics was considered unnecessary. Therefore, the total uncertainty factor was 2. The application of the uncertainty factor of 2 to the HEC results in a recommended guideline of 58 ppm as an 8-hour TWA.

A BMDL of 169 ppm was calculated for the effects on sperm motility in the F_1 males (Table 5.5). In the derivation of an AEL for this endpoint, the BMDL would be adjusted for temporal differences in exposure as discussed above, resulting in a HEC of 177 ppm. For the reasons discussed previously, an uncertainty factor of 3 is considered adequately protective of humans in light of pharmacokinetic similarities between humans and rats and potential pharmacodynamic differences in the response of the human reproductive system (a factor of 3 is used for spermatic endpoints because no data exist that indicate human sperm cells have different susceptibilities compared rat sperm cells). An additional uncertainty factor is also needed to

protect for variability in individual sensitivity across the population[1]. Although workers represent a generally healthy population, relatively common reproductive impairments (e.g., decreased sperm motility, aberrant sperm formation that may result from NPB exposure), would not impact the overt health of the worker and would be largely unobserved, but could result in a decreased reproductive capacity. Further, although data in humans is limited, NBP is structurally similar to isopropylbromide (2BP) which has been shown to cause reproductive toxicity in rodents and humans (Ichihara et al. 1997a, b; Kamijima et al. 1999a, b; Kim et al., 1996, 1999b). Standard risk assessment guidelines state that factors of 3 to 10 should generally be used to account for variation in sensitivity across individuals in the human population. Given the strength of the data base and the extrapolation of the data to occupational exposures, a range of uncertainty factors of 2 to 3 is considered appropriate.

An overall uncertainty factor of 6 to 10 results for the reproductive effects associated with NPB exposure: 3 for differences in pharmacodynamics and between 2 and 3 for the protection of sensitive individuals. Application of this range of factors to the HEC (177 ppm) results in an AEL of 18-30 ppm. Our recommendation is 25 ppm, a midpoint value that accounts for interspecies differences, individual variability, the consistency of adverse effects observed in both animals and humans, the slope of the dose-response curve, the types of reproductive effects observed, the background incidence of the effects, the route of exposure, and pharmacokinetic data. Because uncertainty factors are believed to fall within a lognormal distribution (with the uncertainty factor of 3 representing a half-log value of 10; Dourson et al., 1996), it is actually more accurate to represent the AEL as the midpoint between the uncertainty factors (6-10) in the log scale, which would result in a value of 22 ppm. We chose to select a value of 25 ppm as appropriately protective of human health. Because this AEL is below the value derived from data on liver cell effects, it would be protective of potential hepatic toxicity.

Due to the potential for absorption of NPB through the skin (by analogy to other halogenated solvents), it should be listed with a skin notation; however, due to its high vapor pressure and low blood-air partition coefficient, dermal exposure is unlikely to constitute an appreciable hazard under normal workplace conditions. NPB does not appear to be a skin sensitizer.

[1]This additional uncertainty for sensitive individuals was not factored into the estimation of an AEL derived from data on liver cell effects for several reasons. One is that pre-existing sensitivity to liver toxicity would not be expected to be significant in occupational workers who are otherwise overtly healthy. Second, liver cell vacuolation is commonly found following administration of toxins and is considered to be relatively less significant toxicologically compared to reproductive effects.

Table 5.4
Benchmark Dose-Response Modeling Results

Endpoint	Model	Log-Likelihood	K	AIC	Chi-Square	DF	P-Value	BMR	Risk Type	BMD	BMDL	Reference
Females												
Hepatocellular Centrilobular Vacuolation F_0 Female	GAMMA	-30.324	2	64.65	0.27	3	0.97	0.1	Extra	415.54	319.80	(WIL 2001)
	LOGISTIC	-31.245	2	66.49	1.59	3	0.66	0.1	Extra	430.75	345.09	
	LOGLOGISTIC	-30.421	2	64.84	0.38	3	0.94	0.1	Extra	415.33	319.74	
	PROBIT	-30.748	2	65.50	0.90	3	0.83	0.1	Extra	423.41	334.38	
	LOGPROBIT	-30.219	2	64.44	0.13	3	0.99	0.1	Extra	415.39	322.06	
	MULTISTAGE	-30.651	1	63.30	0.75	4	0.94	0.1	Extra	418.37	312.21	
	WEIBULL	-30.641	2	65.28	0.68	3	0.88	0.1	Extra	411.32	310.50	
Hepatocellular Centrilobular Vacuolation F_1 Female	GAMMA	-20.987	2	45.97	0.33	2	0.85	0.1	Extra	311.57	194.30	(WIL 2001)
	LOGISTIC	-21.571	2	47.14	1.27	2	0.53	0.1	Extra	366.41	288.13	
	LOGLOGISTIC	-21.011	2	46.02	0.35	2	0.84	0.1	Extra	312.17	191.28	
	PROBIT	-21.384	2	46.77	0.99	2	0.61	0.1	Extra	349.45	270.66	
	LOGPROBIT	-20.905	2	45.81	0.21	2	0.90	0.1	Extra	302.24	209.39	
	MULTISTAGE	-21.052	2	46.10	0.37	2	0.83	0.1	Extra	313.46	192.35	
	WEIBULL	-21.036	2	46.07	0.38	2	0.83	0.1	Extra	316.32	191.98	
Males												
Hepatocellular Centrilobular Vacuolation F_0 Male	GAMMA	-28.956	2	61.191	1.46	3	0.69	0.1	Extra	178.42	130.27	(WIL 2001)
	LOGISTIC	-30.774	2	65.55	5.38	3	0.15	0.1	Extra	184.91	139.19	
	LOGLOGISTIC	-28.487	2	60.97	0.41	3	0.94	0.1	Extra	187.64	143.49	
	PROBIT	-31.172	2	66.34	7.64	3	0.05	0.1	Extra	176.00	130.45	
	LOGPROBIT	-28.490	2	60.98	0.56	3	0.91	0.1	Extra	185.34	141.58	
	MULTISTAGE	-30.316	2	64.63	3.53	3	0.32	0.1	Extra	149.90	103.51	
	WEIBULL	-30.013	2	64.03	3.21	3	0.36	0.1	Extra	158.08	110.08	

Table 5.4 (Continued)

Endpoint	Model	Log-Likelihood	K	AIC	Chi-Square	DF	P-Value	BMR	Risk Type	BMD	BMDL	Reference
Hepatocellular Centrilobular Vacuolation F_1 Male	GAMMA	-22.112	2	48.22	1.88	2	0.39	0.1	Extra	141.20	102.25	(WIL 2001)
	LOGISTIC	-23.856	2	51.71	7.50	2	0.02	0.1	Extra	142.80	104.16	
	LOGLOGISTIC	-21.515	2	47.03	0.80	2	0.67	0.1	Extra	152.33	112.22	
	PROBIT	-24.320	2	52.64	6.59	2	0.04	0.1	Extra	132.96	95.44	
	LOGPROBIT	-21.491	2	46.98	0.78	2	0.68	0.1	Extra	145.82	110.33	
	MULTISTAGE	-23.758	2	51.52	4.14	2	0.13	0.1	Extra	119.89	76.46	
	WEIBULL	-23.454	2	50.91	3.52	2	0.17	0.1	Extra	120.79	82.42	
Hepatocellular Centrilobular Vacuolation	GAMMA	-17.937	2	39.87	0.50	3	0.92	0.1	Extra	349.32	227.42	(ClinTrial 1997b)
	LOGISTIC	-18.598	2	41.20	1.59	3	0.66	0.1	Extra	381.63	287.14	
	LOGLOGISTIC	-18.001	2	40.00	0.57	3	0.90	0.1	Extra	348.89	223.95	
	PROBIT	-18.292	2	40.58	1.12	3	0.77	0.1	Extra	369.51	273.39	
	LOGPROBIT	-17.839	2	39.68	0.35	3	0.95	0.1	Extra	344.73	225.49	
	MULTISTAGE	-18.095	1	38.19	0.67	4	0.96	0.1	Extra	345.70	226.13	
	WEIBULL	-18.090	2	40.18	0.71	3	0.87	0.1	Extra	351.38	221.78	
Sperm Motility F_o Males	HILL	-387.393	6	786.79	9.17	1	<0.05	1.1	[a]	393.44	317.56(W)	(WIL 2001)
	POLYNOMIAL	-385.332	5	780.66	5.05	2	0.08	1.1	[a]	386.15	283.38	
	POWER	-384.916	5	779.83	4.21	2	0.12	1.1	[a]	362.43	281.60	
Sperm Motility F_1 Males	HILL	-267.065	6	546.13	--	--	--	1.1	[a]	N/A	N/A	(WIL 2001)
	POLYNOMIAL	-245.698	5	501.40	28.18	1	<0.05	1.1	[a]	330.15	130.70	
	POWER	-232.519	5	475.04	1.83	1	0.18	1.1	[a]	275.76	168.77	

NOTE: AIC is calculated as (-2 * log-likelihood + 2 * K), where K is the number of parameters of the model not estimated at a bound.

[a] Standard deviations from the control mean. (W) indicates that a warning message was given with the estimate, suggesting that its value may not be accurate.

Table 5.5
Summary of BMDS Results for NPB

Endpoint	Model	BMR	Risk Type	BMD	BMDL	Reference
Female						
Hepatocellular Centrilobular Vacuolation F_0 Female	Multistage	0.1	Extra	418.37	312.21	WIL 2001
Hepatocellular Centrilobular Vacuolation F_1 Female	LogProbit	0.1	Extra	302.24	209.39	WIL 2001
Male						
Hepatocellular Centrilobular Vacuolation F_0 Male	Loglogistic	0.1	Extra	187.64	143.49	WIL 2001
Hepatocellular Centrilobular Vacuolation F_1 Male	LogProbit	0.1	Extra	145.82	110.33	WIL 2001
Hepatocellular Centrilobular Vacuolation Male	Multistage	0.1	Extra	345.70	226.13	ClinTrial 1997b
Sperm Motility F_0 Males	Power	1.1	[a]	362.43	281.60	WIL 2001
Sperm Motility F_1 Males	Power	1.1	[a]	275.76	168.77	WIL 2001

[a] Standard deviations from the control mean.

The Center for the Evaluation of Risks to Human Reproduction performed a separate review of the toxicological effects of exposure to NPB (CERHR, 2000). In their report, the Expert Panel developed a BMD, estimating the $BMDL_5$ for reduced pup weight. It is noteworthy that both $BMDL_{10}$ values in our analysis were lower than the $BMDL_5$ value of 305 ppm for a decrease in F_1 pup weight discussed in the CERHR (2002) report.

6. Exposure Assessment

Exposure assessments have been conducted in several industries in which NPB is used as a solvent for adhesive sprays or is used as a degreaser to clean metal parts (Smith 1998a,b,c,d; Reh and Nemhauser 2001; Reh 2000a,b; Reh 2001). In the first of these assessments, workplace monitoring data (8-hour TWA) were obtained by Albemarle Corporation for the use of NPB in adhesive spray and metal cleaning applications under normal worker use conditions (Smith

1998a,b,c,d). Both personal and area samples were collected. Monitoring of personnel was done in the breathing zone of the worker. Area samples also were taken and represent potential exposure levels for employees who are assigned to these work areas, but are not directly involved in the use of NPB. Four adhesive use sites (H, I, J, K) and three metal cleaning sites (D, E, G) were sampled.

Personal samples at four sites using NPB in adhesive spraying applications showed concentrations of 27-34 ppm (n=2), 18-68 ppm (n=4), 32-92 ppm (n=5), and 28-43 ppm (n=4) averaged over an 8-hour period for sites H, I, J, and K, respectively. Area samples collected at adjacent work stations about 10 feet from the NPB spray booths and between two NPB spray booths showed concentrations of 5-11 ppm (n=2) and 17 ppm (n=1), respectively.

At three metal cleaning sites (Sites G, E, D) where NPB is used in a vapor degreaser to clean metal parts, personal samples showed concentrations of <0.1-0.3 ppm (n=3) averaged over 360 minutes (6 hours) for degreaser operators (Site G), 1-5 ppm (n=4) averaged over 7 hours for grinding and motor winding operators (Site E), and an estimated TWA exposure of 30 ppm, without regard to the protection provided by the respirator, for an employee[2] operating a Branson degreaser in an enclosed, separately ventilated room (Site D). Personal samples collected at Site E from shorter duration tasks showed average concentrations of 13 ppm (n=1) over 23 minutes and 5 ppm (n=1) over 40 minutes for final assembly operators, 5-6 ppm (n=2) over 3 hours for grinders, and 42 ppm over 3 hours for an employee in the compressor room.

Area monitoring at Site G showed average concentrations over ~6 hours of 45.9 ppm (collected at the opening of the autobatch degreaser) and <0.1 ppm (collected at control panel of second degreaser using perchloroethylene; also measured 0.4 ppm perchloroethylene). Area monitoring at Site E showed concentrations of 1 ppm and 5-7 ppm over 7 hours and 3 hours, respectively, collected at the back partition of the motor winding department and on top of the work bench shelves in the center of the department, and 4 ppm and 12 ppm over 7 hours and 3 hours, respectively, collected at the Baron Blakslee degreaser, level with the top and 4 feet behind the unit. At Site D, area monitoring in the shop area adjacent to the degreaser room showed concentrations of 3 ppm (n=3) over 6-7 hours, while the concentration inside the degreaser room (on top of the water separator) was 344 ppm over a 6-hour period.

As a follow-up to an employee request and a site visit, NIOSH (Reh and Nemhauser 2001) conducted a visit to Trilithic, Inc., a manufacturer of instrumentation and components for the radio frequency and microwave communications industry, to collect NPB inhalation exposure data. As with the Albemarle facility, NPB is used at Trilithic, Inc. as a degreasing solution for cleaning small parts in a cold batch degreaser. During assembly of small filters, subsystems, and other parts of components, approximately 40 employees over two shifts may need to clean parts using the cold batch degreaser. Degreasing may be performed by any given employee an average of 2-3 times per week.

[2] Workers in the degreasing area put on organic vapor respirators and nitrile gloves before entering the closed room that houses the degreaser. An employee is expected to spend about 1 hour, cumulatively, in a 12-hour shift in the degreaser room.

TWA NPB exposure measurements over a full shift were obtained from 20 assemblers in the Components, Tech Station, Engineering Support, Filters, Custom Filters, and Tunables departments. Measured exposure concentrations ranged from 0.01 to 0.63 ppm, with 13 of the measurements less than the minimum quantifiable concentration of 0.02 ppm. The seven measurements that were greater than 0.02 ppm were from employees using the degreaser at least once during a work shift, with the highest exposure (0.63 ppm) in a worker who used the degreaser twice during a work shift. Two short-term, task-based exposure measurements were taken from multiple employees using the degreaser. Due to the short amount of time any single employee used the degreaser, sampling during degreasing tasks from several employees were combined until the approximate sampling time was 15 minutes. The two task-based NPB exposure concentrations were 2.3 and 8.4 ppm. Area air samples were also collected in the degreasing room and at six areas near the degreasing room. In the degreasing room, a concentration of 4.42 ppm was measured. Five feet from the degreaser, the NPB concentration was 1.7 ppm. In all other areas sampled, concentrations were $\leq$0.02 ppm.

NIOSH (Reh 2000a) collected personal samples from a single 8-hour shift in a cushion manufacturing facility (Marx Industries) in which NPB is the solvent vehicle in the spray adhesive used for gluing together strips of flexible foam used for cushions. There are two foam fabrication lines in which NPB-containing adhesive is spray applied: a Springs Line and a Glue Line. The application areas consist of spray tables interspersed along the length of a conveyor belt, with at least three exhaust fans above each line for vapor removal. The results of the survey focused on the exposure measurements gathered for 16 workers, seven of which were Glue Line sprayers and five were Springs Line sprayers. The remaining four workers consisted of a doffer and a supervisor/set-up person from both the Glue Line and the Springs Line.

The mean NPB exposure concentration for all 16 workers was 96.3 ppm, with individual exposures ranging from 18.1 to 253.9 ppm. Overall, the average exposure was higher among Springs Line workers (118.3 ppm), compared to exposure in the Glue Line workers (79.2 ppm). If only sprayers were considered, the average exposure for the Springs Line was 148.8 ppm, compared to 91.8 ppm for the Glue Line. The mean NPB exposure concentration for all sprayers was 115.6 ppm, with exposures ranging from 57.7 to 253.9 ppm.

Air sampling was also conducted by NIOSH (Reh 2000b) at Custom Products, a company that manufactures seat cushions for the commercial aircraft industry, following recommendations that included the addition of spray booths and local exhaust ventilation for all adhesive spraying operations. In this facility, the production areas are divided into four departments: Saw, Assembly, Sew, and Covers. The foam pieces used to produce cushions are cut with various saws in the Saw department and the foam pieces sprayed with adhesive and pressed together in the Assembly department. Covers are produced from bulk material in the Sew department and the covers placed around the cushions in the Covers department. The workers in the Assembly department are either sprayers or assemblers, while all of the workers in the Covers department are sprayers. A total of six spray booths were installed at all adhesive spraying stations in both the Assembly and Covers departments. An attempt was made to measure full shift inhalation exposures to NPB for all employees in the Assembly, Covers, and Saw departments. In addition, short-term (15-minute) inhalation exposures were collected for sprayers in the Assembly and

Covers departments. Area air sampling was also conducted at various locations and work stations in the Sew department.

Before installation of the spray booths, the overall mean concentration of NPB was 168.9 ppm, with mean exposures in each work area ranging from 117.1 ppm in the Saw area to 197.0 ppm in the Covers area. Following installation of the spray booths, the overall mean NPB exposure concentration was 19 ppm (n=30), with individual measurements ranging from 1.2 to 58 ppm. The highest mean NPB concentration was still in the Covers department (29.2 ppm), followed by the Assembly department (18.8 ppm), and the Saw department (1.8 ppm). The 12 short-term (15-minute) exposure measurements indicated NPB concentrations ranging from 12.3 to 26 ppm in the Assembly department, and 13.4 to 95.8 ppm in the Covers department. Area air sampling at five randomly selected work stations in the Sew department indicated NPB concentrations ranging from 1.1 to 1.9 ppm.

The STN Cushion Company also manufactures sofa cushions for various furniture companies. At STN, adhesive containing NPB is spray-applied using a compressed air spray gun in the Fabrication room, which contains 13 spray stations, each with a slotted local exhaust ventilation hood. Recently, NIOSH (Reh 2001) attempted to measure full-shift inhalation exposures to NPB for all employees in the Fabrication room. Short-term (15-minute) and ceiling (5-minute) inhalation exposure measurements were also collected for sprayers, as well as area air sampling in the Fabrication room and adjacent rooms (Saw and Poly rooms).

A total of 14 full-shift personal exposure measurements were collected from 12 sprayers and two floaters. The average NPB exposure concentration for the sprayers was 65.9 ppm, with exposures ranging from 41.3 to 143.0 ppm. NPB exposures for the two floaters were 8.7 and 19.4 ppm. The nine short-term NPB exposure measurements obtained from sprayers ranged from 33.7 to 173.9 ppm, with ceiling exposures (n=11) ranging from 39.5 to 151.9 ppm. Area air sampling indicated NPB concentrations of 7.2, 7.7, and 1.7 ppm in the Fabrication, Saw and Poly rooms, respectively.

Concentrations of NPB greater than the proposed AEL of 25 ppm have been measured in several of the above facilities, mainly in areas in which spray application of NPB-containing adhesive is performed. If the proper engineering controls are instituted, however, as with the spray booths installed at Custom Products (Reh 2000b), average exposure concentrations may be reduced by approximately an order of magnitude, bringing exposures below the recommended AEL of 25 ppm.

7. Discussion

Before the completion of the recent two-generation reproductive study for NPB (WIL 2001), there were several areas of uncertainty regarding the toxicity of NPB. These uncertainties included the potential for reproductive toxicity and, to a lesser extent, carcinogenicity. The concerns surrounding the potential reproductive toxicity of NPB were based on the lack of reproductive/developmental studies and the reported effects of the related compound 2BP. The available two-generation reproductive study now addresses these concerns and provides

quantitative information for assessing the potential reproductive toxicity of NPB and is the basis for the current AEL.

In the event of occupational exposures to levels of NPB above the recommended AEL, occupational monitoring for potential spermatic and hepatic effects would be prudent. Also, as mentioned in Section 4, the fact that NPB is metabolized to bromide, an anesthetic with a long half-life in the human, should be considered when developing an occupational monitoring program for NPB.

8. References

Barber E.D., Donish W., Mueller K. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames *Salmonella*/microsome assay. Mutat Res 90:31-48.

Barber E., Donish W. 1982. An exposure system for quantitative measurements of the microbial mutagenicity of volatile liquids in genotoxic effects of airborne agents. Environ Sci Res 25:3-18.

CERHR. 2002. NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of 1-Bromopropane. National Toxicology Program. NTP-CERHR-1-BP-02. March 2002.

ClinTrials. 1997a. A 28-Day Inhalation Study of a Vapor-Formulation of ALBTA1 in the Albino Rat. Report No. 91189. Prepared by ClinTrials BioResearch Laboratories, Ltd., Senneville, Quebec, Canada. May 15, 1997. Sponsored by Albemarle Corporation, Baton Rouge, LA.

ClinTrials. 1997b. ALBTA1: A 13-Week Inhalation Study of a Vapor Formulation of ALBTA1 in the Albino Rat. Report No. 91190. Prepared by ClinTrials BioResearch Laboratories, Ltd., Senneville, Quebec, Canada. February 28, 1997. Sponsored by Albemarle Corporation, Baton Rouge, LA.

Crump K. 1995. Calculation of benchmark doses from continuous data. Risk Anal 15:79-89.

Dourson, M. L., Velazquez, S.F., and Robinson, D. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. Regul Tox Pharm 24:108-120.

Elf Atochem S.A. 1993. Acute Oral Toxicity in Rats. N-Propyl Bromide. Study No. 10611 Tar. Study Director, Jack Clouzeau. Study performed by Centre International de Toxicologie, Miserey, France. November 3, 1993.

Elf Atochem S.A. 1994. Ames test - reverse mutation assay on *Salmonella typhimurium*. n-Propyl Bromide. HIS1005/1005A. Study performed by Sanofi Recherche, Service de Toxicologie.

Elf Atochem S.A. 1995a. Micronucleus Test by Intraperitoneal Route in Mice. N-Propyl Bromide. Study No. 12122 MAS. Study Director, Brigitte Molinier. Study performed by Centre International de Toxicologie, Miserey, France. September 6, 1995.

Elf Atochem S.A. 1995b. Acute Dermal Toxicity in Rats. N-Propyl Bromide. Study No. 13113 Tar. Study Director, Stephane de Jouffrey. Study performed by Centre International de Toxicologie, Miserey, France. September 26, 1995.

Elf Atochem S.A. 1995c. Skin Sensitization Test in Guinea-Pigs (Maximization method of Magnusson B, and Kligman, A.M.). N-Propyl Bromide. Study No. 12094 TSG. Study Director, Stephane de Jouffrey. Study performed by Centre International de Toxicologie, Miserey, France. June 30, 1995.

Elf Atochem S.A. 1996. Amendment to Protocol. N-Propyl Bromide. Study No. 13293 MLY. Amendment No. 01. Study Director, Brigitte Molinier. January 29, 1996.

Elf Atochem S.A. 1997. Study of Acute Toxicity on n-Propyl Bromide Administered to Rats by Vapour Inhalation. Determination of the 50% Lethal Concentration. L.E.T.E. Study Number 95122. Study performed by Laboratoire d'Etudes de Toxicologie Experimentale.

Fueta Y., Ishidao T., Kasai T., et al. 2000. Decreased paired-pulse inhibition in the dentate gyrus of the brain in rats exposed to 1-bromopropane vapor. J Occup Health 42:149-151.

Gargas M.L., Burgess R.J., Voisard D.E., Cason G.H., Andersen M.E. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98:87-99.

Haseman J.K., Lockhart A. 1994. The relationship between use of the maximum tolerated dose and study sensitivity for detecting rodent carcinogenicity. Fundam Appl Toxicol 22:382-391.

Hermann H., Vial J. 1935. Nouvelles syncopes cardiaques par association toxique de l'adrenaline et de divers produits organiques volatils. C R Soc Biol 119:1316-1317 (As cited in Zakhari and Aviado, 1982).

Ichihara G., Asaeda N., Kumazawa T., Tagawa Y., Kamiuima M., Yu X., Kondo H., Nakajima T., Kitoh J., Yu I.J., Moon Y.H., Hisanaga N., Takeuchi Y. 1996. Testicular toxicity of 2-bromopropane. J Occup Health 38:205-206.

Ichihara, G.; Yu, S.; Kamijima, M.; Ting, X.; Wu, X.; Takeuchi, Y. 1997a. Occupational health Survey on Workers Exposed to 2-Bromopropane at Low Concentrations. American Journal of Industrial Medicine. 35:523 - 531.

Ichihara G., Asaeda N., Kumazawa T., et al. 1997b. Testicular and hematopoietic toxicity of 2-bromopropane, a substitute for ozone layer-depleting chlorofluorocarbons. J Occup Health 39:57-63.

Ichihara M., Takeuchi Y., Shibata E., Kitoh J., et al. 1998. Neurotoxicity of 1-Bromopropane. Translated by Albemarle Corporation.

Ichihara G., Jong X., Onizuka J., et al. 1999. Histopathological changes of nervous system and reproductive organ and blood biochemical findings in rats exposed to 1-bromopropane. Abstracts of the 72nd Annual Meeting of Japan Society for Occupational Health. May 1999. Tokyo.

Ichihara G., Yu X., Kitoh J., et al. 2000a. Reproductive toxicity of 1-bromopropane, a newly introduced alternative to ozone layer depleting solvents, in male rats. Toxicol Sciences 54:416-423.

Ichihara G., Kitoh J., Yu, X., et al. 2000b. 1-Bromopropane, an alternative to ozone layer depleting solvents, is dose-dependently neurotoxic to rats in long-term inhalation exposure. Toxicol Sciences 55:116-123.

Japan Bioassay Research Center. Inhalation and reproduction toxicity on rats by 1-BP repeated dose. Unpublished abstract.

Jones A.R., Walsh D.A. 1979. The oxidative metabolism of 1-bromopropane in the rat. Xenobiotica 9:763-772.

Kamijima M., Ichihara G., Yu X., et al. 1997a. Disruption in ovarian cyclicity due to 2-bromopropane in the rat. J Occup Health 39:3-4.

Kamijima M., Ichihara G., Kitoh J., et al. 1997b. Ovarian toxicity of 2-bromopropane in the nonpregnant female rat. J Occup Health 39:144-149.

Khan S., O'Brien P.J. 1991. 1-bromoalkanes as new potent nontoxic glutathione depletors in isolated rat hepatocytes. Biochem Biophys Res Commun 179:436-441.

Kim H.-Y., Chung Y.-H., Jeong J.-H., Lee Y.-M., Sur G.-S., Kang J.-K. 1999a. Acute and repeated inhalation toxicity of 1-bromopropane in SD rats. J Occup Health 41:121-128.

Kim Y, Park J, Moon Y. 1999b. Hematopoietic and reproductive toxicity of 2-bromopropane, a recently introduced substitute for chlorofluorocarbons. Toxicol Lett. Sep 5;108(2-3):309-13.

Kim Y., Jung K., Hwang T., Jung G., Kim H., Park J., Kim J., Park J., Park D., Park S., Choi K., Moon Y. 1996. Hematopoietic and reproductive hazards of Korean electronic workers exposed to solvents containing 2-bromopropane. Scand J Work Environ Health 22:387-391.

Maeng S.H., Yu I.J. 1997. Mutagenicity of 2-bromopropane. Ind Health 35:87-95.

Oh B., Kaneko H., Sato A. 1998. Effects of 1-BP to the translation of beta-amyloid protein in mouse brain comparison between young mouse and adult mouse. Translated by Albemarle Corporation.

Reh C.M. 2000a. Health Hazard Evaluation for Marx Industries, Inc. Letter from Christopher M. Reh to Mark Kiser dated February 1, 2000.

Reh C.M. 2000b. Health Hazard Evaluation for Custom Products, Inc. Letter from Christopher M. Reh to Stuart Patch dated December 21, 2000.

Reh C.M. 2001. Health Hazard Evaluation for Thomasville (STN). Letter from Christopher M. Reh to Steve Cothran dated March 7, 2001.

Reh C.M., Nemhauser, J.B. 2001. Health Hazard Evaluation Report 2000-0233-2845, Trilithic, Inc., Indianapolis, Indiana, January, 2001.

Rodwell D.E. 2001. A Developmental Toxicity Study in Rat Via Whole Body Inhalation Exposure. Conducted by Huntingdon Life Sciences, Study No. 98-4141. Sponsored by Brominated Solvents Consortium. August 23, 2001.

Saito-Suzuki R., Teramoto S., Shirasu Y. 1982. Dominant lethal studies in rats with 1,2-dibromo-3-chloropropane and its structurally related compounds. Mutat Res 101:321-327.

Sekiguchi S., Suda M., Zhai Y.L., Honma T. 2002. Effects of 1-bromopropane, 2-bromopropane, and 1,2-dichloropropane on the estrous cycle and ovulation in F344 rats. Toxicol Lett 126:41-49.

Smith R.L. 1998a. "Site E Assessment." Fax transmission from Robert Smith, Albemarle Corporation to EPA, April 22, 1998.

Smith R.L. 1998b. "Exposure Assessment for Site D." Fax transmission from Robert Smith, Albemarle Corporation to EPA, April 23, 1998.

Smith R.L. 1998c. "Exposure Assessment for Site G." Fax transmission from Robert Smith, Albemarle Corporation to EPA, April 24, 1998.

Smith R.L. 1998d. "Air Monitoring for Adhesive Applications." Fax transmission from Robert Smith, Albemarle Corporation to EPA, June 26, 1998.

Stelljes M. 2001. Memo from Mark Stelljes to Richard Morford. Human in vitro bioassays conducted by EnviroMed Laboratories. April 2, 2001.

Takeuchi Y., Ichihara G., Kamijima M. 1997. A review on toxicity of 2-bromopropane: mainly on its reproductive toxicity. J Occup Health 39:179-191.

U.S. Environmental Protection Agency (US EPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F. Office of Health and Environmental Assessment, Washington, DC. October 1994.

U.S. Environmental Protection Agency (US EPA). 1995. The use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007. Risk Assessment Forum, Washington, DC. February 1995.

U.S. Environmental Protection Agency (US EPA). 1999. Guidelines for Carcinogen Risk Assessment. NCEA-F-0644. Review Draft. Risk Assessment Forum, Washington, DC. July, 1999.

U.S. Environmental Protection Agency (US EPA). 2000. BenchMark Dose Software. National Center for Environmental Assessment with technical support from the National Health & Environmental Effects Research Laboratory. www.epa.gov.ncea/bmds.htm.

Wang H., Ichihara G., Yamada T. et al. 1999. Subacute effects of 1-bromopropane on reproductive organs and the nervous system. Abstracts of the 72nd Annual Meeting of Japan Society for Occupational Health. May 1999. Tokyo.

WIL 2001. An Inhalation Two-Generation Reproductive Toxicity Study of 1-Bromopropane in Rats. Conducted by WIL Research Laboratories, Inc., Sponsored by Brominated Solvents Consortium. May 24, 2001.

Williams T., Kelley C. 1997. GNUPLOT 3.7 Beta. (As cited in US EPA 2000).

Yu X, Ichihara G, Kitoh J, Xie Z, Shibata E, Kamijima M, Takeuchi Y. 2001. Neurotoxicity of 2-bromopropane and 1-bromopropane, alternative solvents for chlorofluorocarbons. Environ Res 85(1):48-52.

Zakhari S., Aviado D.M. 1982. Cardiovascular toxicology of aerosol propellants, refrigerants, and related solvents. In: Van Stee EW, Ed. Cardiovascular Toxicology. Raven Press, New York. pp. 281-326.

Zhao W., Aoki K., Xie T., Misumi J. 1999. Electrophysiological changes induced by different doses of 1-bromopropane and 2-bromopropane. J Occup Health 41:1-7.